Activity 3

Molecular Medicine Comes of Age

At a Glance

Focus: Students discover some of the benefits of understanding human genetic variation at the molecular level by assuming the roles of employees of two fictional pharmaceutical companies to solve problems related to the development of new drugs.

Major Concepts: One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and treat disease. The development of effective gene-based therapies is an exciting outcome of human genetic research. These therapies, however, are potentially many years away for many diseases.

Objectives: After completing this activity, students will

- appreciate that identifying and sequencing disease-related genes helps scientists better understand and treat disease;
- be able to explain that our increasing understanding of how genetic differences among people affect response to drug treatment will change how physicians prescribe drugs in the future;
- be able to explain how understanding the molecular structure of a disease-related gene can help scientists develop new strategies for treating the disease; and
- recognize that as our understanding of human genetic variation improves, we likely will see many changes in how physicians diagnose and treat human diseases.

Prerequisite Knowledge: Students should understand the relationship among DNA, RNA, protein, and amino acids as well as how to interpret data displayed in tables.

Basic Science-Health Connection: This activity highlights the contribution that scientists studying human genetic variation at the molecular level are making to modern medicine. Research in genetics has made many contributions to clinical medicine across the last century. Research associated with the Human Genome Project is significantly changing not only how we think about human disease, but how we treat it.

Introduction

Activity 3, *Molecular Medicine Comes of Age*, and Activity 4, *Are You Susceptible?*, focus students' attention on the practical, medical applications of understanding human genetic variation at a molecular level.

Activity 3 uses two vehicles—variable responses to drugs and the development of treatment strategies targeted at a disease's biochemical mechanism—to highlight some of the ways scientists can use molecular information to improve disease treatment. That is, Activity 3 focuses on those portions of Figure 6 that deal with pharmacogenomics and targeted drug therapy. An extension to Activity 3 invites students to consider gene therapy as another strategy made possible by a knowledge of molecular genetics.

Geneticists long have known that there is individual variation in the response to certain drugs. For example, in the early part of the 20th century, both Archibald Garrod and J.B.S. Haldane suggested that biochemical individuality as a function of genetic variation might explain people's unusual reactions to drugs and food. By the middle of the 20th century, biologists had identified several clear associations between certain genotypes and adverse drug reactions, including adverse reactions by some people to the drug succinylcholine, which is used as a muscle relaxant during surgery. If treated with this drug, individuals who produce a variant of the enzyme pseudocholinesterase, which normally metabolizes the drug, are in danger of extended depression of respiratory muscles and can suffer prolonged periods of apnea (cessation of breathing), which can be fatal. This is but one example of adverse drug reactions; a study reported in the 15 April 1998 issue of the *Journal of the American Medical Association* found that as many as 106,000 hospitalized patients per year had *fatal* adverse reactions to drugs. This would rank such reactions between the fourth and sixth leading causes of death in the United States.

Biologists also have long known that understanding the molecular structure of a disease-related gene can help them identify potential targets for intervention. As described in *Understanding Human Genetic Variation*, a striking example of this approach to combating disease is recent work on cystic fibrosis. Cystic fibrosis is the most common fatal genetic disease in the United States, affecting approximately 30,000 people. Currently, about half of those affected die by age 30. Since the identification in 1989 of the gene that is altered in cystic fibrosis, the pace of basic research has increased rapidly, and scientists are optimistic that they will be able to translate new knowledge about the molecular basis of the disease to new strategies to improve patients' lives.

In this activity, students assume the roles of employees of two fictional pharmaceutical companies. Each company, Firm A and Firm B, is facing a significant challenge related to the development of a new drug. Firm A is developing a drug to treat asthma. Unfortunately, preliminary test results show variable and unpredictable effects. Student working as employees of Firm A must discover an explanation for these results and recommend a course of action. As students investigate this problem, they learn about the relationship between genetic variation and individual responses to drugs, and discover one way in which pharmaceutical companies are beginning to deal with this issue.

In contrast, Firm B wants to develop a new drug to treat cystic fibrosis. Students working as employees of Firm B discover first that most current treatments for this disease address its symptoms and not its cause. Students are then challenged to identify as many points as possible at which the biochemical processes underlying this disease could be corrected.

As students investigate this problem, they learn that knowing the sequence of a disease-related gene and understanding the disease's biochemical basis can help scientists develop exciting new approaches to treatment.

Because the benefits expected from both pharmacogenomics and targeted drug therapy are still largely unrealized, this activity is a bit futuristic and you may

wish to acknowledge this to students. It is clear, however, that the era of molecular medicine—the application of knowledge about the molecular basis of variation to treating human disease—already is upon us. Although molecular medicine is just beginning to develop, the field has enormous potential for the improvement of personal and public health.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 3.1, *Molecular Medicine Comes of Age* (make 1 overhead transparency)
- Masters 3.2–3.5, *Saving Firm A* (make 1 copy of each master for each team that will complete this part of the activity)
- Master 3.6, *Report Form for Firm A* (make 1 copy per student who will complete this part of the activity and 1 overhead transparency)
- Master 3.7, *Some New Genetic Data (Firm A)* (make 1 copy per team)
- Masters 3.8–3.11, *Saving Firm B* (make 1 copy of each master for each team that will complete this part of the activity)
- Master 3.12, *Report Form for Firm B* (make 1 copy per student who will complete this part of the activity and 1 overhead transparency)
- Master 3.13, *Some New Information (Firm B)* (make 1 copy per team)

Procedure

1. **Introduce the activity by displaying a transparency made from Master 3.1, *Molecular Medicine Comes of Age,* and asking students what they think the statement means and whether they can think of any specific examples that illustrate or provide evidence for this point.**

   Students should be able to explain that understanding human genetic variation at a molecular level means identifying the specific differences in base sequence that distinguish one human from another. Although students likely will not mention pharmacogenomics and targeted drug therapy as examples of health care strategies that depend on understanding molecular variation, they may mention gene therapy as a strategy.

   Students may have difficulty expressing these ideas in their own words. You may wish to help them by asking probing questions such as "What does it mean to understand human genetic variation at a molecular level?" and "Can you think of any way in which finding and sequencing the gene related to a disease could help scientists develop ways to treat it?"

Asking students to explain the phrase "understand human genetic variation at a molecular level" will help you assess what they learned from the first part of Activity 2.

2. **Explain that the students' challenge in this activity is to investigate two examples that illustrate and provide evidence for this point. Explain further that students will investigate these examples by acting as teams of employees in two pharmaceutical companies that are facing problems that threaten the companies' futures.**

3. **Divide the class in half and explain that one half of the class will act as employees in Firm A and the other half will act as employees in Firm B. Tell**

students that the problems the two firms face are different, but both problems can be solved in ways that relate to the statement on the transparency.

4. **Direct students to organize into their teams. Distribute one copy each of Masters 3.2, 3.3, 3.4, and 3.5, *Saving Firm A, [Role],* to each team in one half of the class and one copy each of Masters 3.8, 3.9, 3.10, and 3.11, *Saving Firm B, [Role],* to each team in the other half. Also distribute one copy of Master 3.6, *Report Form for Firm A*, or Master 3.12, *Report Form for Firm B,* to each student and explain that the students should use these forms to organize their discussions and to report the results of their work.**

   As an alternative to using the masters provided for Firm A, you can have students use the equivalent videos on the *Human Genetic Variation* CD-ROM. Follow the instructions on page 23 to load the CD-ROMs onto the computers students will use.

5. **Instruct the students to decide in their teams who will assume each of the four roles associated with their problem and to distribute the masters accordingly.**

6. **Give the teams 30 minutes to complete their reports and to be ready to defend their analysis of their company's problem and their suggested solution to the class, using the appropriate *Report Form* to organize their thoughts.**

   When students reach Step 6 on the *Report Form* (Master 3.6 or Master 3.12), they will ask you, as vice president for the company, for additional data (Master 3.7, *Some New Genetic Data,* or Master 3.13, *Some New Information*). You can give the teams copies of the masters or you can simulate some mechanism that requires students to search for these data.

   If students use the videos on the *Human Genetic Variation* CD-ROM instead of the masters provided for Firm A, they will need to view the video *Some New Genetic Data* when they reach Step 6. Access to the video is password protected. You will need to give students the password: **gene**.

An interesting way to assess students' understanding of this information is to ask one team to offer an answer to a question, and then ask a different team to evaluate the answer's accuracy and completeness and propose corrections or additions as necessary. This technique helps students learn to offer feedback in a positive way and extends accountability for acceptable answers to more students than simply the team members who provide the initial answer.

7. **After the designated time, call the class to order. Explain that you will assume the role of the vice president for research for Firm A first and then the role of the vice president for research for Firm B, and that you are calling everyone together to hear the results of the teams' work.**

8. **Display a transparency made from *Report Form for Firm A* and use it to guide the discussion by asking teams from Firm A to present their answers to the questions (a different team should answer each question). After one team has offered an answer, invite questions and additional comments from the class.**

   To keep all students involved in both discussions, invite students from the other firm to contribute to the discussion by asking questions and even offering suggestions, as appropriate.

Question 1 What is the biological problem facing Firm A with respect to Drug X?

There is an inconsistent response to Drug X among asthma patients, that is, the drug does not work the same way on all patients.

Question 2 Describe asthma in your own words (refer to the *Team Coordinator* and *Physiologist* handouts).

Asthma is a fairly common condition that involves breathing difficulties. The bronchioles contract abnormally. It often is associated with an allergic reaction to foreign substances.

Question 3 What is Drug X designed to do for asthma sufferers (refer to the *Team Coordinator* and *Physiologist* handouts)?

The drug opens up the bronchioles so that the asthma patient can breathe more easily.

Question 4 Look at the preliminary test results (refer to the *Biostatistician* handout). Can you predict which group will be helped most or least by Drug X? For example, does the sex of the individual make a difference? Does having pets make a difference? Explain your answers.

No. There is no way to make a prediction, because there is no pattern in the response to the drug. Neither the sex of the individual nor the presence of pet dander makes a difference in the response.

Question 5 What does the example of ApoE (refer to the *Molecular Biologist* handout) suggest might be happening with Drug X? Based on this example, what might Firm A investigate?

The data indicate that response to the Alzheimer drug might be based on variations in the ApoE gene. Perhaps Firm A should explore genetic differences with respect to response to Drug X.

Question 6 Firm A's vice president for research (your teacher) will provide you with some new data. What do the new data reveal about Drug X?

There is a difference in response to the drug on the basis of the genetic variations in the patient population.

Question 7 What would be an appropriate way to prescribe Drug X?

It would be appropriate to test each asthma patient for his or her genotype to determine whether Drug X will be effective with that individual.

Question 8 Has your team solved the biological problem facing the company with respect to Drug X? What new problems has it raised?

The team's work has answered the basic biological question about response to Drug X. It has raised new questions about the ability to test all asthma sufferers. For example, how expensive is it to do that? Will physicians order the test? Will it be covered by health insurance? Who will have access to the information that results from the genetic test? How will Firm A educate physicians and other health care professionals so they understand the test and the results and so they can explain this information to their patients?

9. Repeat the same process with the teams from Firm B, but use a transparency made from Master 3.12 to guide the discussion.

Again, to keep all students involved in the discussion, invite students from the other firm to contribute to the discussion by asking questions and even offering suggestions, as appropriate.

Question 1 What is the problem facing Firm B with respect to Drug Y (refer to the *Team Coordinator* handout)?

Drug Y is a successful treatment for cystic fibrosis (CF) and is the firm's leading product. Firm B needs to keep looking ahead, however, and begin thinking about new treatments for CF that take advantage of what scientists have learned about the condition and, in the future, might be able to supplement or even replace income that the company is now receiving from Drug Y.

Question 2 Describe cystic fibrosis in your own words (refer to the *Physiologist* handout).

CF is a genetic disease that causes the body to produce an abnormally thick, sticky mucus. This mucus clogs the airways and other ducts and passages in the body and provides an ideal breeding ground for many microorganisms. CF patients have frequent airway infections and often show poor weight gain and slowed growth and development.

Question 3 What have we learned in the past few years about the cause of CF (refer to the *Molecular Biologist* handout)?

The most common CF mutation leads to one missing amino acid in the CFTR protein. The loss of this single amino acid causes the protein to be misshapen in such a way that most of it is destroyed instead of being inserted into the cell membrane. The absence of properly functioning CFTR protein in the cell membrane leads to abnormal movement of chloride ions and water in and out of the cell and production of thick, sticky mucus.

Question 4 What is Drug Y (and most other current treatments) designed to do for CF patients (refer to the *Physician* handout and discuss what goes in the last column of the table provided)?

Most existing treatments for CF focus on alleviating the symptoms of the disease, for example, removing airway mucus, reducing infection, and improving nutrition. Students should discover this by completing the last column in the table provided on the *Physician* handout.

Question 5 Firm B's vice president for research (your teacher) will provide you with some new information. What clue does this new information provide about how Firm B might approach developing new treatments for CF?

The important clue that students should gain from this new information is that understanding the biological basis of CF has allowed these researchers to propose a way to correct the problem in CF cells. This is a different approach to treatment than treating its consequences.

Question 6 What new approaches do you recommend Firm B consider as it attempts to design and develop one or more new treatments for CF?

Students will not be able to suggest detailed approaches to developing treatments, but they should be able to propose general approaches that address each of the items on the flow chart on the *Molecular Biologist* handout. For example, students might suggest developing treatments that would correct or replace the defective CF genes; replace the missing amino acid in the CFTR protein; cause the CFTR protein to fold properly despite the missing amino acid; prevent the defective CFTR protein from being destroyed before it reaches the cell membrane; introduce functional CFTR protein into the cell from another source; or create another mechanism in the cell that would regulate the movement of chloride ions.

Question 7 Has your team solved the problem facing the company with respect to Drug Y? What new problems has it raised?

No, the team has not "solved the problem" facing the company, but it has suggested several directions that the company may want to investigate as it develops new CF treatments. New problems that the team's work has raised include problems common to all development of new drugs: deciding on an approach to try, allocating funds to pay for development and clinical testing, and going through the process of gaining FDA approval for the new treatment.

10. Challenge the students to generalize what they have learned by answering the following questions:

- **How is genetic variation related to the use of drugs?**

  Students should understand that genetic differences between people may cause them to respond differently to therapeutic drugs. As scientists begin to detect such genetic differences, physicians will become more sensitive to individual variation in response to drugs and may

You may wish to ask the students who worked on Firm A's problem to answer the questions related to Firm B's problem, and vice versa.

even begin to prescribe drugs based on differences in genotype.

- **How will pharmaceutical companies likely use our increasing understanding of human genetic variation?**

  Pharmaceutical companies may begin to design drugs that are intended for people who have certain genotypes. They also may resurrect products that were not viable in the past because of their unpredictable, negative side effects on certain people.

- **How can discovering the genes associated with genetic disorders help scientists develop new approaches to treatment?**

  As Figure 6 shows, mapping and cloning the genes associated with genetic disorders helps scientists discover their underlying biochemical mechanisms, and this can suggest new approaches to treatment.

Refocusing students' attention on the opening statement draws them back to the activity's major concept.

Another way to raise these issues with students is to display a transparency made from Figure 6 and ask students to explain how the activity they just completed relates to the beginning and end points of the arrows on the diagram.

11. **Display again the transparency you made from *Molecular Medicine Comes of Age*. Ask students to explain what it means and provide examples that illustrate or provide evidence for this point.**

12. **Close the activity by asking students what they think the transparency's title means.**

Potential Extensions

Extend this activity by assigning teams of students to listen to and report on selected talks from the fall 1998 *Campus on the Mall* series co-sponsored by the National Human Genome Research Institute, the National Institutes of Health, and the Smithsonian Institute. Available on the Web at http://www.nhgri.nih.gov/DIR/VIP/SI/, this series of slide-illustrated audio lectures provides the layperson with an insider's tour of recent genetic research and a glimpse into the medicine of the future.